EBioMedicine 11 (2016) 29–30

Contents lists available at ScienceDirect

EBioMedicine

journal homepage: www.ebiomedicine.com

Commentary

Chronic Whiplash-Associated Disorders: Reorganization of the Brain?

Iris Coppieters MSc, PT [a,b,*], Anneleen Malfliet MSc, PT [a,b,c]

[a] Department of Rehabilitation Sciences and Physiotherapy, Faculty of Medicine and Health Sciences, Ghent University, Belgium
[b] Pain in Motion International Research Group, Belgium
[c] Department of Physiotherapy, Human Physiology and Anatomy (KIMA), Faculty of Physical Education & Physiotherapy, Free University Brussels, Belgium

ARTICLE INFO

Article history:
Received 5 August 2016
Accepted 5 August 2016
Available online 9 August 2016

A wide range of human brain imaging techniques has provided the opportunity to explore in vivo the neurophysiological processes of the brain (Schmidt-Wilcke, 2015; Baliki and Apkarian, 2015). This neuroimaging research has shown neuronal plasticity, which refers to the possibility of the central nervous system including the brain to adapt but also to maladapt structure, function and organization (Davis and Moayedi, 2013). Subsequently, the role of maladaptive brain alterations in the persistent complaints of various chronic pain conditions (e.g., fibromyalgia, chronic low back pain, temporomandibular disorders) has been gradually elucidated (Schmidt-Wilcke, 2015; Baliki and Apkarian, 2015; Davis and Moayedi, 2013). Emerging evidence indicates that different chronic pain conditions are each associated with distinct brain reorganization, which is referred to as the neural pain signature (Kucyi and Davis, 2015). In addition, changes in resting state interactions between brain networks implicated in default states, salience, attention, and reward have been demonstrated in chronic pain patients (Baliki and Apkarian, 2015; Kucyi and Davis, 2015). The results of longitudinal imaging studies suggest that brain alterations are involved in the transition to chronic pain (Hashmi et al., 2013). In particular, the corticolimbic circuitry, which is a key system for reward and motivated behavior, has been reported as a mediator for this transition (Vachon-Presseau et al., 2016).

Although it can be hypothesized that brain alterations also play a role in the complex persistent complaints of patients with chronic whiplash-associated disorders (WAD), these changes remain poorly investigated. Therefore, the **study of Vállez García et al. (2016)**, recently published in *EBioMedicine*, is of great scientific and clinical importance because they examined possible alterations in regional cerebral blood flow (rCBF) in female patients with chronic WAD (n = 12) compared to healthy pain-free women (n = 8) by using $H_2^{15}O$ positron emission tomography (PET). Brain function, which reflects the amount of 'activity' that the brain generates, can be measured via its blood perfusion and/or metabolism by using PET with intravenous injection of a radiopharmaceutical tracer such as $H_2^{15}O$ (Fox et al., 1984). Active brain regions have a higher need of oxygen and glucose, which is reflected in higher perfusion and/or metabolism.

The present commentary article focuses on the contribution of the study of Vállez García et al. (2016) to the literature, discusses the paper in the context of current research, highlights unanswered questions and addresses recommendations for future research.

The case-control study of Vállez García et al. (2016) correctly raises our attention to the necessity of examining brain alterations in chronic WAD, which is a prominent gap in current literature. Nevertheless, reorganization of the brain is possibly the missing cornerstone for understanding the pathophysiology of chronic WAD and for advancing pain treatment. The authors hypothesized that the close interaction between the neck and midbrain structures through fibers originating from the C1–C3 spinal segments that project to the periaqueductal grey (PAG) and the thalamus (Vállez García et al., 2016) could be the missing key. We believe this is indeed one possible piece of the puzzle for understanding chronic WAD, however, we want to alert that also alterations in (resting state) functional brain connectivity and activity, and structural alterations in cortical and subcortical grey matter regions and white matter tracts could contribute to chronic pain and associated complaints in these patients. In contrast to their hypothesis, Vállez García et al. could not detect significant alterations in rCBF in the PAG (Vállez García et al., 2016), which is a midbrain structure believed to be involved in brain-orchestrated descending pain modulation (Davis and Moayedi, 2013). Nevertheless, this hypothesis is plausible, as dysfunctional pain modulation is a key symptom of patients with chronic WAD. On the contrary, the authors demonstrated altered rCBF in limbic (Hashmi et al., 2013) and corticolimbic (Vachon-Presseau et al., 2016) brain regions and regions that are involved in various aspects of pain processing (Schmidt-Wilcke, 2015; Davis and Moayedi, 2013). Previous brain imaging studies in other chronic musculoskeletal pain patients such as chronic low back pain and fibromyalgia have likewise observed functional but also structural alterations in these regions (e.g. thalamus, insula, precuneus, parahippocampal and posterior cingulate gyrus) compared to controls (Schmidt-Wilcke, 2015; Davis and Moayedi, 2013).

Furthermore, Vállez García et al. correlated the rCBF of the regions that presented significant perfusion differences with subjective scores

DOI of original article: http://dx.doi.org/10.1016/j.ebiom.2016.07.008.
* Corresponding author.
URL: http://www.paininmotion.be (I. Coppieters), http://www.paininmotion.be (A. Malfliet).

http://dx.doi.org/10.1016/j.ebiom.2016.08.010

on the Neck Disability Index (NDI), Hospital Anxiety and Depression Scale (HADS), Whiplash Disability Questionnaire (WDQ), and the electrical perception and pain thresholds measured at the second and sixth cervical spinal processes (Vállez García et al., 2016). This is important as these measures represent subjective pain experience and are cost-effective in the context of clinical practice. The authors reported significant correlations between the rCBF in the right precuneus, right insula, and right superior temporal lobe, although to different extents, with the scores obtained from the NDI, HADS, WDQ and the electrical perceptions and pain thresholds (both positive and negative correlations) in the chronic WAD group. However, it is not clear from the manuscript if these are weak, moderate or strong correlations. Yet, the observed correlations are of clinical importance because they emphasize the existence of a relationship between clinical symptoms in chronic WAD patients and regional perfusion alterations in the brain.

Additionally, we believe it would have been valuable to investigate the presence of disturbed conditioned pain modulation (CPM) or inefficient descending pain inhibition in the chronic WAD group compared to controls. Subsequently, the efficacy of CPM could have been correlated with the rCBF of regions critically involved in descending pain inhibition such as the PAG (Davis and Moayedi, 2013). Knowledge on these relations is important to further unravel the mechanisms of persistent pain.

Alterations in brain perfusion in patients with chronic WAD compared to healthy controls using PET imaging have only been demonstrated by two other studies (Linnman et al., 2009; Otte et al., 1997). These studies included, in accordance to the present study, rather small sample sizes ($n = 18$ and $n = 39$). Linnman et al. (2009) analyzed rCBF using ^{15}O PET and found alterations in the parahippocampal and posterior cingulate gyrus, and thalamus in the chronic WAD group, which is according to the results of Vállez García et al. Furthermore, they observed alterations in regions which were not detected by Vállez García et al. (Linnman et al., 2009). Otte et al. used FDG (^{18}F) PET and only demonstrated hypometabolism in parieto-occipital regions in chronic WAD patients (Otte et al., 1997). However, Otte et al. did not examine regional hyperperfusion. Interestingly, Vállez García et al. (2016) showed in a subanalysis also hypoperfusion in the posterior parietal occipital region. The latter result indicates that the previously reported alterations in this region have been underestimated and that maybe the brain is trying to compensate for this hypoperfusion by hyperperfusion in adjacent areas (Vállez García et al., 2016).

Future research: The study by Vállez García et al. (2016) advances our understanding of chronic WAD and provides researchers and clinicians with innovative insights into the role of the brain in chronic WAD, however, only focused on alterations in rCBF. Because of the cross-sectional nature of the study, no conclusions can be drawn about the causal relationship between chronic pain and rCBF alterations. Consequently, there remain various critical questions that the field has yet to address regarding chronic pain in chronic WAD. What is the causal relationship between brain imaging results and the development and maintenance of persistent pain? Who is vulnerable to developing chronic pain and what underlies this vulnerability? To which structural and functional extent is the brain altered, measured with sophisticated MRI techniques, and what is the relation between brain alterations, and various clinical measures? Besides the chicken and the egg discussion, it will be a challenge for researchers to explore the effectiveness of different therapy strategies for chronic WAD patients by analyzing the effects of specific interventions on brain alterations as well as on clinical measures by using a longitudinal design.

Key messages: The paper of Vállez García et al. (2016) provides innovative insights and confirmation of previously determined findings on the presence of rCBF alterations in brain regions involved in affective, motivational and cognitive processing of pain, and in regions part of the (cortico)limbic system in female patients with chronic WAD compared to healthy pain-free women. Furthermore, clinical important relations between rCBF alterations, and pain intensity, pain perception, pain-related disability, anxiety and depression were revealed. These results should impart to both scientists and clinicians, the knowledge that brain alterations possibly play a role in the persistent complaints of patients with chronic WAD. However, further research is absolutely warranted to unravel the specific role of the brain with the ultimate endeavour to improve pain treatment and to decrease suffering from pain.

Disclosures

Iris Coppieters is funded by the Special Research Fund of Ghent University (BOF-Ghent).

Anneleen Malfliet is funded by the Agency for Innovation by Science and Technology (IWT) — Applied Biomedical Research Program (TBM), Belgium.

The authors declare that no conflicts of interest exist.

References

Baliki, M.N., Apkarian, A.V., 2015. Nociception, pain, negative moods, and behavior selection. Neuron 87, 474–491.

Davis, K.D., Moayedi, M., 2013. Central mechanisms of pain revealed through functional and structural MRI. J. NeuroImmune Pharmacol. 8, 518–534.

Fox, P.T., Mintun, M.A., Raichle, M.E., Herscovitch, P., 1984. A noninvasive approach to quantitative functional brain mapping with H_2 (15)O and positron emission tomography. J. Cereb. Blood Flow Metab. 4, 329–333.

Hashmi, J.A., Baliki, M.N., Huang, L., Baria, A.T., Torbey, S., Hermann, K.M., Schnitzer, T.J., Apkarian, A.V., 2013. Shape shifting pain: chronification of back pain shifts brain representation from nociceptive to emotional circuits. Brain 136, 2751–2768.

Kucyi, A., Davis, K.D., 2015. The dynamic pain connectome. Trends Neurosci. 38, 86–95.

Linnman, C., Appel, L., Soderlund, A., Frans, O., Engler, H., Furmark, T., Gordh, T., Langstrom, B., Fredrikson, M., 2009. Chronic whiplash symptoms are related to altered regional cerebral blood flow in the resting state. Eur. J. Pain 13, 65–70.

Otte, A., Ettlin, T.M., Nitzsche, E.U., Wachter, K., Hoegerle, S., Simon, G.H., Fierz, L., Moser, E., Mueller-Brand, J., 1997. PET and SPECT in whiplash syndrome: a new approach to a forgotten brain? J. Neurol. Neurosurg. Psychiatry 63, 368–372.

Schmidt-Wilcke, T., 2015. Neuroimaging of chronic pain. Best Pract. Res. Clin. Rheumatol. 29, 29–41.

Vachon-Presseau, E., Centeno, M.V., Ren, W., Berger, S.E., Tetreault, P., Ghantous, M., Baria, A., Farmer, M., Baliki, M.N., Schnitzer, T.J., Apkarian, A.V., 2016. The emotional brain as a predictor and amplifier of chronic pain. J. Dent. Res. 95, 605–612.

Vállez García, D., Doorduin, J., Willemsen, A.T., Dierckx, R.A., Otte, A., 2016. Altered regional cerebral blood flow in chronic whiplash associated disorders. EBioMedicine 10, 249–257.